REMARKS

Applicants have amended the claims to more particularly define the invention taking into consideration the outstanding Official Action. Claim 1 has been amended to remove the "optional" aspect of the claim and restrict the claim subject matter so that antibodies are reversibly bound to the antigens for a displacement reaction to further distinguish the claimed subject matter from the prior art. This amendment is made without prejudice or disclaimer and Applicants retain the right to further prosecution this aspect of the invention in a further application. Claim 17 has been amended as fully supported by Applicants' specification at page 6, lines 11-13. Applicants most respectfully submit that all of the claims now present in the application are in full compliance with 35 U.S.C. 112 and are clearly patentable over the references of record.

The present invention provides a coated metal surface on a solid support, wherein the coating consists of a protein layer that is firmly attached to the metal surface, the protein layer being coupled to linker molecules that are bound to low molecular weight antigens, wherein the linker molecules contain between the functional groups, via which they are coupled to the protein layer, respectively bound to the antigen, an aliphatic hydrocarbon chain of 1, 2, or 3 carbon atoms.

The coated surface provided by the present invention is for use in a displacement reaction where the affinity of the antibody to the antigen that is bound on the coated surface via the linker has to be lower than the affinity to the antigen in the test solution. More than three carbon atoms in the aliphatic chain results in a stronger affinity between the antibody and the on the coating bound antigen, which does not promote a displacement reaction. The affinity of the antibody to the antigen bound on the coated surface has to be weaker than that to the antigen in the test solution, otherwise a sufficient displacement of antibodies bound to antigens on the coated surface by antigens in the test solution will not take place, thus resulting in no detection/determination or very poor detection/determination of the antigens in the test solution.

The rejection of claims 1-3, 5, 6, 12, 13, and 15-18 under 35 U.S.C. 103(a) as being unpatentable over Miura et al. in view of Jacobs et al. further in view of Johnson has been carefully considered but is most respectfully traversed in view of the amendments to the claims and the following comments.

As noted above, the coated surface provided by the present invention is for use in a displacement reaction where the affinity of the antibody to the antigen that is bound on the coated surface has to be lower than the affinity to the antigen in the test solution. More than three carbon atoms in the aliphatic chain results in a stronger affinity between the antibody and the on the coating bound antigen, which does not promote a displacement reaction. The affinity of the antibody to the antigen bound on the coated surface has to be weaker than that to the antigen in the test solution, otherwise a sufficient displacement of antibodies bound to antigens on the coated surface by antigens in the test solution will not take place, thus resulting in no detection/determination or very poor detection/determination of the antigens in the test solution. This reaction, which is fundamental to the claimed invention, is opposite to that taught by Miura and is clearly not suggested to one of ordinary skill in the art to which the invention pertains.

In this regard, it is most respectfully submitted that the Official Action has misinterpreted the teachings of the Miura reference. The biological reaction suggested in Miura is a typical competition reaction, as opposed to the current invention which is concerned with a displacement reaction. A competition reaction is a variant of so-called weight gain reaction, whereas a displacement reaction is a weight loss reaction. In the Miura reference the antibody and antigen, e.g. morphine, are mixed before the introduction into the flow cell having the sensing element.

In the current invention, the coated metal surface of claim 1 may be a sensing element in the flow cell is pre-coated with the weak immunocomplex between antigen and antibody before introduction of the sample that might contain the antigen, e.g. morphine. This means that one skilled in the art need not mix the sample with the antibody before introduction into the flow cell, and at introduction of sample the

presence of antigen in the sample solution gives a displacement of antibodies from the sensing surface, i.e. a weight loss.

In paragraph [0013] of Miura, the procedure for indirect measuring the medical substance (antigen) is described in general terms. Applicants will try to clarify the teaching of this paragraph for a better understanding of the differences between the presently claimed subject matter and the reference. .

a)The antigen is preliminarily fixed to the resonance material (sensing element) and a resonance value (angle) is registered.

b) **A known amount** of **antibody** having a higher molecular weight than the antigen is contacted with the antigen preliminarily fixed to the resonance material and a different resonance value (angle) than in a) is obtained due to the amount of antibody coupled to the fixed antigen (weight gain).

c) **A known amount** of **antibody** is mixed with and reacted to a sample liquid, which contain the antigen (sample liquid).

d) The sample liquid in c), which now contains both free antibody as well as antigen-antibody complex is contacted with the resonance material (sensing element)

e) The residue of antibody (**free antibody**) that has **not reacted** with the sample antigen **will now couple to the antigen on the sensing element (weight gain).**

f) The difference in resonance level (weight gain) between b) and e) is a measure of the amount of antigen that has reacted in c)

As will be very clear from the above, one of ordinary skill in the art will appreciate that there is no displacement of antibody from antigen involved, only firm attachment (weight gain) and this does not suggest the presently claimed invention. The Official Action refers specifically to some paragraphs of Miura to show the similarities with the current claim 1, and Applicants have the following detailed comment on each paragraph.

A metal surface on a solid support (thin metal film formed on a prism support par. 6). *This is correct.*

The coating consists of a protein layer firmly attached to the metal surface (BSA, paragraph 22 and 43). No protein is mentioned in [22] on the metal film, and in [43] is disclosed how antibodies directed to a medical substance are produced by coupling said substance to a protein, BSA, to produce an immunogen thereto, which is cultivated. Applicants most respectfully submit that one of ordinary skill in the art would probably believe that Miura means that the BSA-antigen conjugate is used as an immunogen for immunization of mice for production of antibodies.

And the protein layer coupled to linker molecules that are bound to low molecular weight antigens (par. 22 and 50; antigens are low molecular weight, par 41).

No protein layer coupled to linker molecules are mentioned in [22] only direct or indirect coupling of antigen, and in [50] ***attachment*** *of* ***antigen onto a protein*** *on a metal film by* ***absorption*** *is suggested as well as* ***chemically coupling*** *the* ***antigen*** *to the* ***metal film*** *after coupling of a functional group having affinity for the metal film to the antigen has been done.*

It is correct that paragraph 41 mentions low molecular weight antigens. Thus, no linker molecules have been suggested here!

Wherein the linker molecules are coupled to protein layer and are bound to the antigen (par. 105-110). *This has* ***not been disclosed*** *in paragraphs [105 -110], but production of an antigen-protein conjugate and fixing said conjugate onto a metal film followed by introduction of antibody to study the relation between concentration of antibody and the amount of change of the resonance angle.*

And wherein the antigens are reversibly bound to antibodies specific for antigens wherein the antibodies are more weakly bound to the immobilized antigens than an analyte antigen to be tested for displacement of antibody from the immobilized antigen (antibodies are bound to antigens on substrate, and are reversibly bound because the antibodies can be displaced during a competition assay and therefore the antibodies are more weakly bound than an analyte because the antibodies can be displaced by analyte, par 81). As can be seen in Figure 13 a weight gain is recorded in both cases (antibody alone and antibody+MO). Displacement is always a weight loss situation.

Applicants most respectfully submit that *the paragraph [0081] is not very clear, but Applicants refer to Applicants' initial explanation of the competition assay. Please note that no displacement of antibody is described anywhere in this cited US application, which has subsequently been abandoned.*

In summary, Miura et al, US 2002/0009812 does not disclose any displacement of antibody from an antigen. Therefore this reference does not disclose or suggest anything related to the presently claimed invention.

Please note that BSA is not a monoclonal antibody but a the protein Bovine Serum Albumin as opposed to the comments on page 5 line 7 referring to par.81 of Miura et al.

Jacobs et al. discloses a protein layer on a substrate surface and a linker with functional groups (NHS-Y-NHS), however, as previously admitted by the Examiner there is no mention of what the length of Y is or for that matter if the Y is an aliphatic hydrocarbon chain at all. In addition, there is whatsoever no mention of the significance of the affinity between the antibodies, the antigens bound on the coated surface and the antigens in the test solution or displacement reactions. On the contrary, the impression that a skilled person in the art gets when reading the disclosure of Jacobs is that there it is implicitly indicated that the affinity of the antibody to the antigen bound on the protein layer has to be strong in order to achieve the desired test results.

The newly cited reference Johnson US 5,631,172 is concerned with metal ion-ligand coordination complexes, antibodies directed thereto and assays using such antibodies, and there are no teachings of what kind of linkers between a protein layer on a solid support and a low-molecular weight antigen would be suitable for immunoassays where antibodies reversibly bound to said antigens are dissociated and displaced by sample antigens. Moreover, the portion cited in the Official Action represents a preference based on Applicants' specification which is impermissible even under KSR. There is no rational basis or sound reasoning for the conclusion that the claimed subject matter is obvious from the combined teachings of the prior art relied upon in the rejection. The Johnson reference, at lines 33-35, state that Q and B are linking moieties consisting of from 0-50 carbon and heteroatoms, and there is no teaching to the specific for the linker is set forth in the claims.

This is particularly true in view of the unexpected results shown in the present specification that only shorter aliphatic chains of less than 4 carbon atoms produces unexpected results of a significant displacement of antibody upon exposure to the analyte. Reference is made to page 8, last two paragraphs to page 9, first paragraph of the specification which discusses these advantages. Applicants also most respectfully direct the Examiner's attention to MPEP § 2145 wherein it is stated that Office personnel should consider all rebuttal argument and evidence presented by Applicants and the citation of In re Soni for error in not considering evidence presented in the specification. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claim 4 and 14 under 35 U.S.C. 103(a) as being unpatentable over Miura et al. in view of Jacobs et al. further in view of Johnson et al., as applied to claim 1, further in view of Houser et al., has been carefully considered but is most respectfully traversed in view of the amendments to the claims and the above comments. The teachings of the Houser et al reference does not overcome the deficiencies in the primary references as discussed above. Accordingly, it is most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all the claims now present in the application are most respectfully requested.

Respectfully submitted,
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